REMARKS/ARGUMENTS

Reexamination and reconsideration of this Application, withdrawal of the rejections, and formal notification of the allowability of all claims as now presented are earnestly solicited in light of the above amendments and remarks that follow.

Claims 1-28, 30-44, 46-48, 50-53, 55, 56, 58, and 60 are pending in the application. Claims 54, 57, and 59 have been cancelled without prejudice or disclaimer. Independent claims 1, 32, 48, and 52 have been amended to recite that the administering step comprises injecting the hydrogel matrix into one or more locations in the area of the dermal/subdermal tissue junction beneath the ulcer or at the periphery of the ulcer. This subject matter was previously set forth in claims 54, 57, and 59, which are now cancelled. Applicant respectfully submits that no new matter is introduced by these amendments.

Applicant appreciates the Examiner's time and attention during a telephonic interview on August 11, 2009. During the interview, both remaining double patenting rejections were discussed. The undersigned noted that neither cited patent claims any particular method of administration of the hydrogel matrix, and also fails to recite ulcer treatment. In addition, the undersigned noted that evidence of record suggests that the route of administration is a highly important part of the invention. Mere treatment with the matrix in a topical application was demonstrated to be ineffective in treating diabetic ulcers, which are notoriously difficult to treat in any event. The Examiner agreed to consider these arguments when presented in an office action response.

Claims 1-29, 31-42, 46-48, 50-60 stand rejected under the doctrine of obviousness-type double patenting as being unpatentable over either the claims of U.S. Patent No. 6,261,587 or U.S. Patent No. 6,713,079, in view of the Miller reference, as well as the Davis and Pickart references. Applicant respectfully traverses these rejections.

First, Applicant notes that neither cited patent claims a method of treating the type of chronic ulcers recited in the present application, which are known in the art to be extremely difficult to treat. Many diabetic ulcers can remain open for many years despite aggressive wound treatment. In contrast to the present invention, the '079 patent merely claims a method of "promoting wound healing" and the '097 patent merely claims a method of "stimulating

vascularization." Thus, there is a clear distinction between the patient population that is contemplated in each patent and the patient population of the present invention.

Additionally, the route of administration set forth in each claim of record is distinct from anything claimed in either cited patent. Neither cited patent claims any particular method of administering the hydrogel matrix. In contrast, all claims of record recite injecting the hydrogel matrix into one or more locations in the area of the dermal/subdermal tissue junction beneath the ulcer or at the periphery of the ulcer. There is simply nothing in the claims of the cited patents, or even in their specifications, that suggest injecting a matrix in the area of the dermal/subdermal tissue junction beneath or at the periphery of the ulcer.

It is respectfully submitted that the above distinctions should be sufficient to prevent the application of an obviousness-type double patenting rejection based on either reference. There are clear distinctions between the claims of the invention and the claims of the cited art that would negate a finding of obviousness. Both the claimed patient population and the claimed route of administration are completely missing from the claims of the cited patents. These significant distinctions between the claims of the cited patents and the pending claims weigh heavily against a finding of obviousness. Accordingly, for at least these reasons, Applicant respectfully requests reconsideration and withdrawal of this rejection.

In addition, Applicant notes that the claims of the '587 patent are particularly distinct from the claims of the present invention because only stimulation of vascularization is claimed in the patent. It has been demonstrated in the art that not all "vascularizing" agents are beneficial treatment options for ulcers. In fact, there is at least one known vascularizing agent that has been tried as a diabetic foot ulcer treatment and failed. In Chapter 18 of Levin and O'Neal's "The Diabetic Foot" (6th Edition), David Steed notes in Chapter 18 (entitled *Modulating Wound Healing in Diabetes*) that fibroblast growth factors (FGFs) "act as angiogenesis factors by stimulating growth of new blood vessels through proliferation of capillary endothelial cells" (p. 399). However, Steed goes on to admit that there are "no clinical trials that have proven FGF to be of benefit in clinical wound healing."

In addition, Applicant directs attention to the Richard *et al.* reference appearing in a 1995 issue of the journal *Diabetes Care*. In the Richard reference, a study of the use of FGF as a treatment for chronic neuropathic foot ulcers in diabetic patients is described. As noted on the first page (p. 64), the researchers stated that FGF performed no better than a placebo in reducing ulcer perimeter and area, and concluded that application of FGF has no advantage over a placebo for healing chronic neuropathic diabetic ulcers of the foot. Two other studies are mentioned on page 67 in the Richard reference. In one, a complex mixture of numerous ingredients significantly improved healing of chronic diabetic ulcers. However, no conclusion related to the rejections of record can be drawn from this study since there is no way to determine if the perceived healing effect is at all linked to a vascularizing agent. In the second study, bFGF was reported to enhance wound healing "slightly, but nonsignificantly" (emphasis added). Viewing the Richard reference as a whole, the inescapable conclusion is that the use of growth factors such as bFGF to treat chronic diabetic wounds is nothing more than unproven and "controversial" (page 67, middle column), and even the authors conclude that the profound healing defect of diabetes may explain the failure of bFGF to demonstrate beneficial effect (page 68). As a result, Applicant views the obviousness rationale with regard to the '587 patent to be particularly weak, and requests reconsideration and withdrawal of the rejection based on the '587 patent for this additional reason.

Still further, Applicant respectfully submits that an obviousness analysis under *Graham v. John Deere Co.* must include evaluation of objective indicia of non-obviousness, such as so-called "secondary considerations" including evidence of unexpected results. It is respectfully submitted that the record includes considerable evidence of unexpected and surprising results. First, it is again noted that the prior art recognizes the intractability of chronic diabetic ulcers, even in the face of aggressive wound care. In an article in Journal of Wound Care (Vol. 17, No. 10, 2008; copy attached), White and McIntosh note that standard diabetic ulcer treatment can average 12-20 weeks with no more than a 31% healing rate after 20 weeks, meaning about 70% of diabetic foot ulcers remain unhealed after 20 weeks of treatment using standard treatment methods (page 431, first paragraph of second column).

Despite the grim statistics associated with standard ulcer treatment and the failure of at least one known vascularizing agent to treat such ulcers, the present application presents data in Example 3 of incredible results associated with use of the present invention to treat diabetic foot ulcers. Patient 103 described on page 13 was successfully treated with matrix injections that resulted in complete closing of the ulcer in only 14 days, despite the fact that the ulcer had previously failed to respond to standard wound care and DERMAGRAFT treatment (a dermal graft made from human fibroblast cells) and had persisted for four years. Patient 108 presented with an ulcer that had persisted for 12 years, yet the ulcer was fully closed by Day 56 after treatment with matrix injections. Patient 109 presented with a two-year-old ulcer that was dramatically reduced in size following matrix injection treatment after 56 days. This ulcer was non-responsive to numerous aggressive treatment methods, including APLIGRAF (a bi-layered dermal graft material), REGRANEX (a topical gel containing platelet-derived growth factor), and 30 days in a hyperbaric oxygen chamber.

Additionally, in the declaration of Dr. Ronald Hill and the accompanying Exhibit A submitted previously, a study of the use of the hydrogel matrix to treat diabetic ulcers in dogs is described. The study report presented in Exhibit A notes that initial treatment of two ulcers consisted of topical application of the hydrogel matrix or injection of the matrix though a catheter sutured into the wound. The study report indicates that neither application route resulted in improved wound healing. Only injection of the matrix into the subcutaneous space around and across the lesion resulted in healing. See page 5 of Exhibit A.

In sum, the intrinsic record includes evidence of extraordinary success in treating diabetic ulcers resistant to even aggressive graft therapy. The method of the invention has been shown to significantly diminish ulcer size even in ulcers that have persisted for many years. In addition, the claimed route of administration has been shown to be important for successful ulcer treatment. Topical administration of the hydrogel matrix, which is the preferred route of prior art ulcer treatment, has been shown to be ineffective for ulcer treatment using the claimed hydrogel matrix. This is surprising as it is clear that prior art attempts to treat such ulcers focus on wound dressings and topical graft materials. For example, White and McIntosh list numerous types of topical wound dressings and the present application references a number of additional topical

treatments, such as those marketed under the names DERMAGRAFT, REGRANEX, and APLIGRAF. However, no injectable treatments are mentioned in the attached Journal of Wound Care article. In addition, in Chapter 18 of Levin and O'Neal's "The Diabetic Foot" (6th Edition), David Steed refers to various growth factors that are topically applied to an ulcer, but does not discuss treatment by injection. In the Richard reference of record, bFGF was applied topically in the studies described therein. It is also noted that the Miller reference relied upon by the Examiner fails to disclose any injectable treatments. Accordingly, the record is replete with evidence of unexpected results associated with treatment of chronic ulcers with hydrogel matrix injections. The claimed route of administration by injection has also been shown to be surprisingly important for successful treatment, which is counter-intuitive to the prior art. Prior attempts to treat diabetic ulcers overwhelmingly focus on topical administration of wound dressings, growth factors, and graft materials. In light of the foregoing, Applicant respectfully submits that the claimed invention is not obvious in light of the claims of either cited patent, and reconsideration and withdrawal of both rejections is requested.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

/christopher m. humphrey/

Christopher M. Humphrey
Registration No. 43,683

Customer No. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 862-2200
Fax Raleigh Office (919) 862-2260

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